
IN THE NAME OF GOD

FIBROBLAST GROWTH FACTOR 23 AND CHRONIC KIDNEY DISEASE

BY

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FGF23
The new hormone of the bone/kidney axis

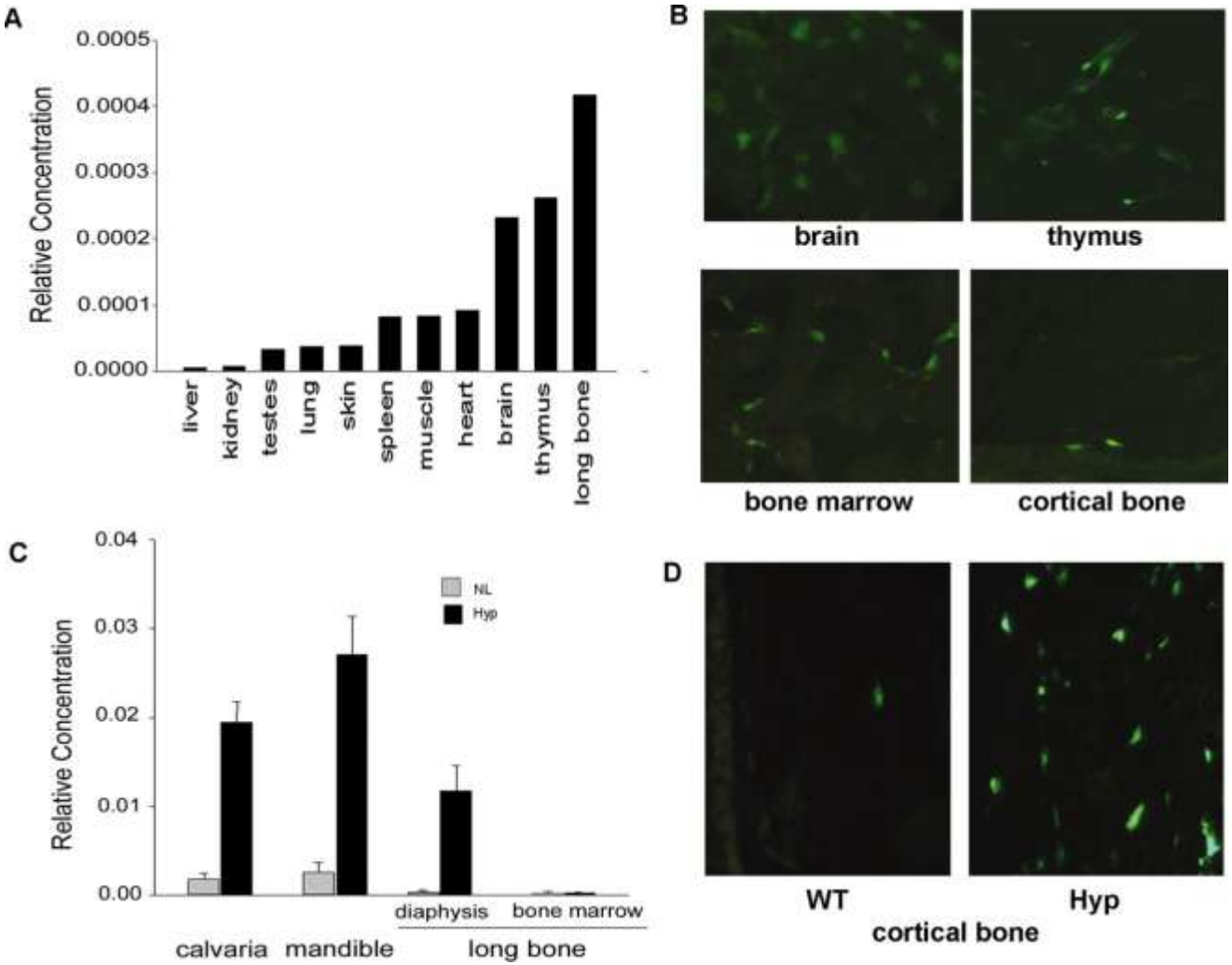
First described in the early 2000's

A protein synthesized by bone Osteocytes, Osteoblasts

FGF23

Is predominately expressed in osteocytes in bone , but it is also expressed in
venous sinuses in the bone marrow,
in the ventrolateral thalamic nucleus,
in thymus
and lymph nodes

Tissue expression of fibroblast growth factor 23 (FGF23).



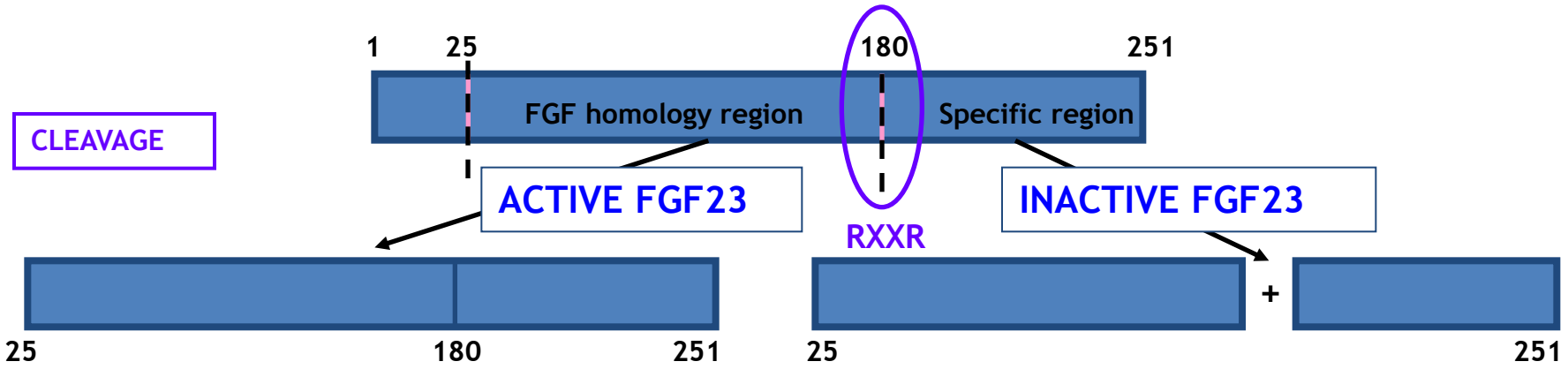
Shiguang Liu, and L. Darryl Quarles JASN 2007;18:1637-1647

FGF23, biochemical and structural properties

Protein - 251 amino-acids, 30 kDa

FGF19 subfamily, the ‘endocrine’ FGFs

Two forms: active/inactive



Klotho

One of the three goddesses of the Moirae*, who in Greek mythology

(spins the thread of life)

She is the goddess who helps life to unfold,

In contrast

The (apoptotic) goddess Atropos, who cuts the thread of life

*__Moirae__ - any of the three Greek goddesses of fate or destiny

Klotho

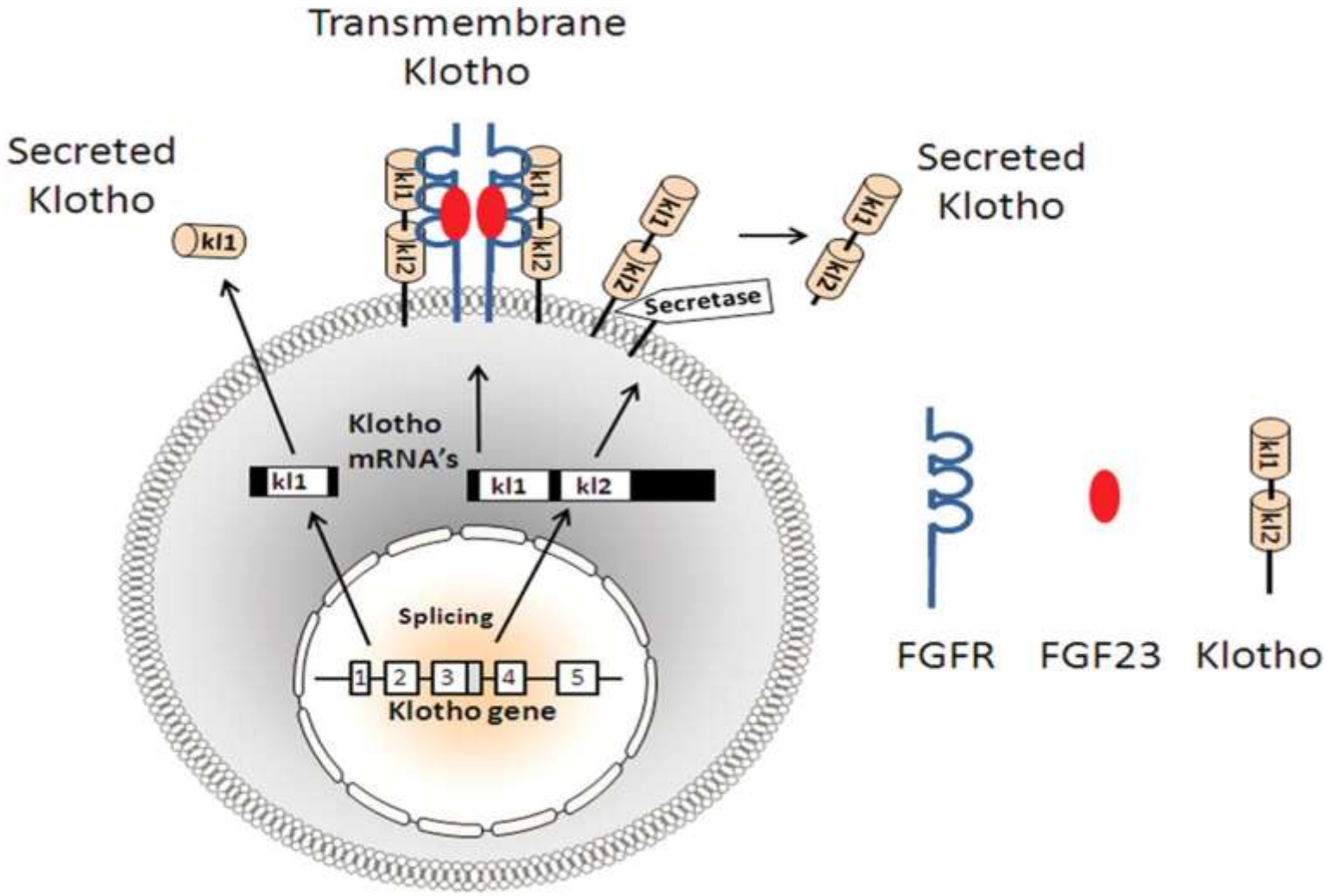
Is a transmembrane protein that has recently been shown to be required for FGF23 activation

Klotho functions as an obligatory coreceptor for FGF23

FGF23, in the absence of klotho, cannot exertits bioactivities

Kidney Int. 2008 ; 74(5): 566–570

Schema for Klotho gene, transcripts and proteins.



Hu M C et al. Nephrol. Dial. Transplant. 2012;27:2650-2657

NDT Nephrology Dialysis Transplantation

Regulation of FGF23 signaling by Klotho

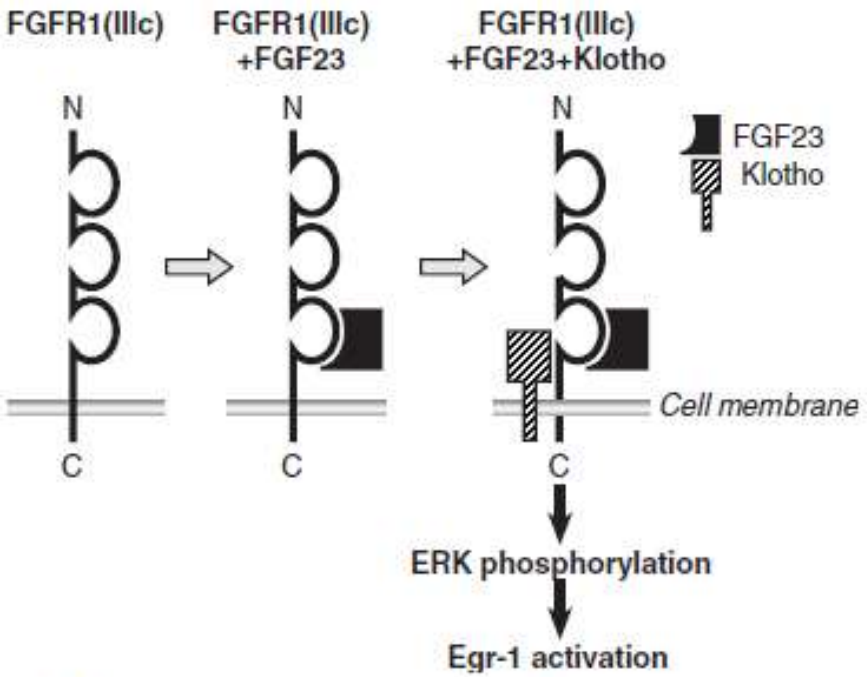


Fig. 2. Schematic view of the interaction between FGF23, Klotho and their receptor, FGFR1(IIIc).

Nephrol Dial Transplant 2007; 22: 1524–1526

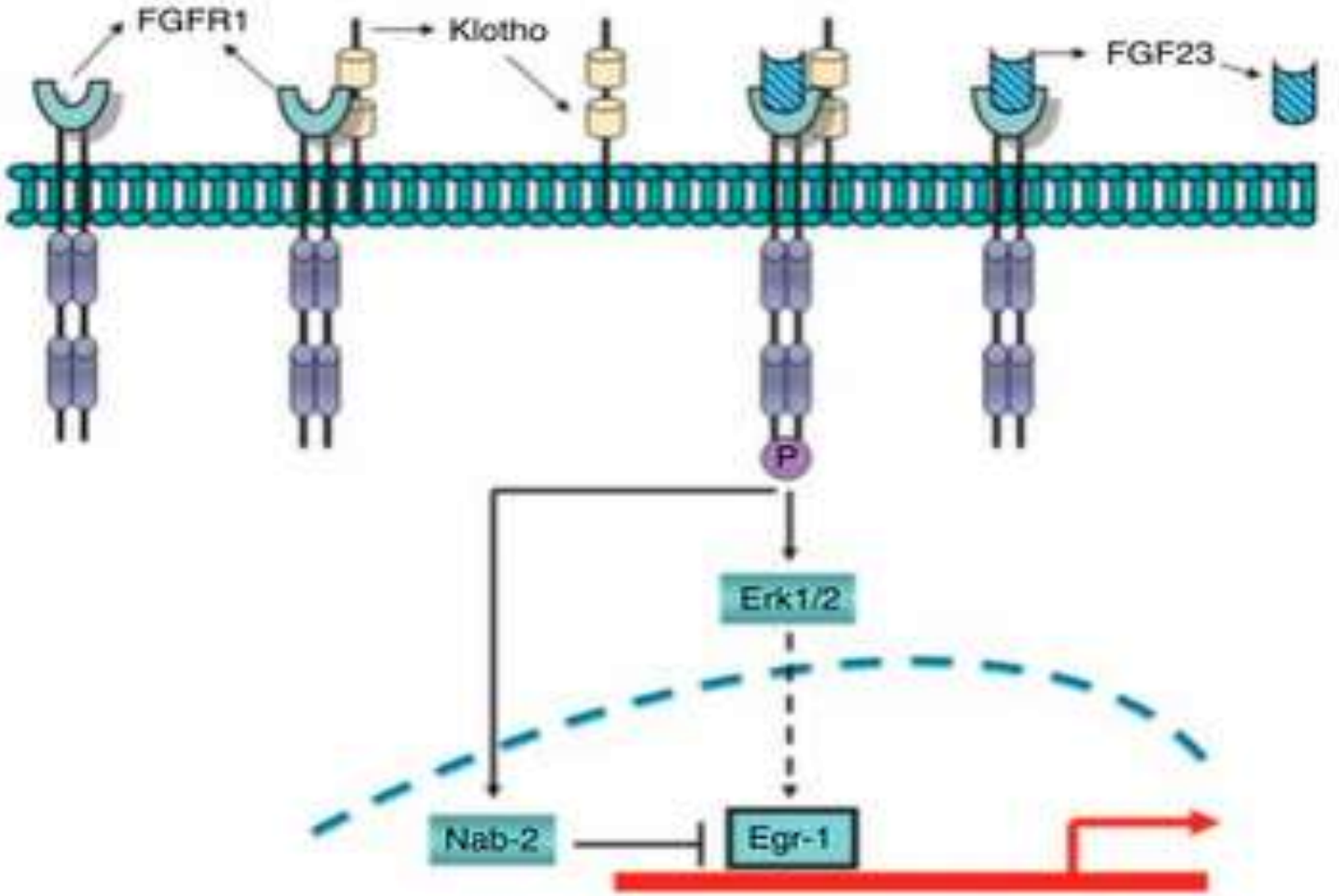


Figure 3 Schematic outline of FGF23–FGFR interactions. Signaling of FGF23–FGFR involves klotho as a cofactor to induce such downstream signaling molecules as Erk1/2, which could influence the activation of Egr-1. FGF23 also induces Nab-2 (Fukuda *et al.* 2007), specific corepressor of Egr-1 that could suppress the transcriptional activity of Egr-1, and thereby establish a negative feedback loop to regulate physiological activities of FGF23.

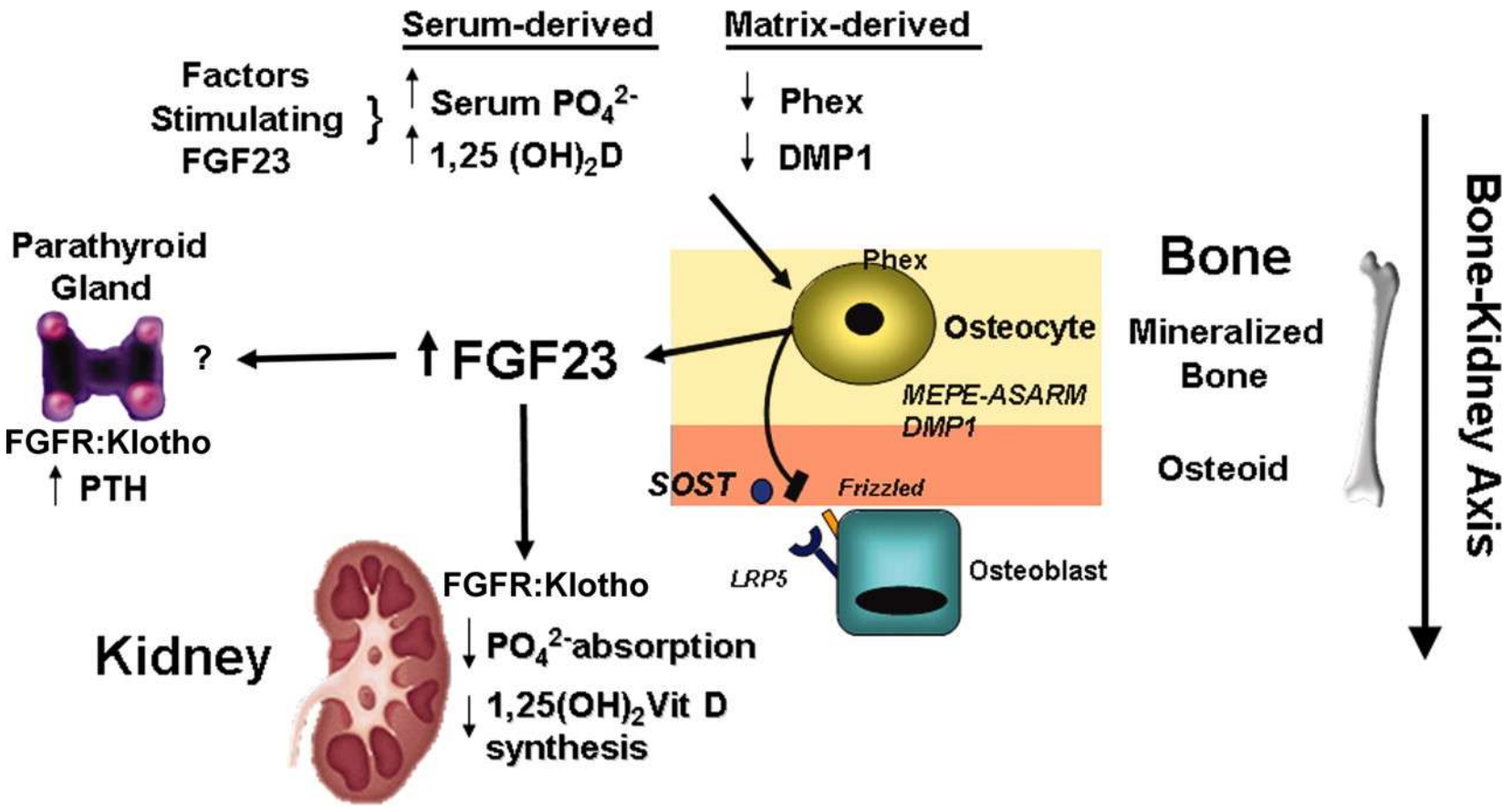
Klotho binds to multiple FGFR and increases their affinity to FGF23.

Klotho-FGFR coexpression likely defines the tissue specificity of FGF23 effects .

The coexpression of widely expressed FGFR - Klotho implicates the
kidney,
parathyroid gland,
pituitary gland,
and choroid plexus
as possible targets for FGF23

In contrast,
the absence of Klotho in
bone,
lung,
liver,
skin,
spleen,
small intestines,
and adrenal gland suggests that these tissues are
not targets for FGF23

The bone–kidney axis.



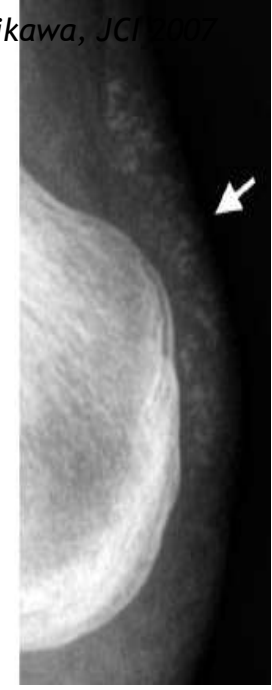
Shiguang Liu, and L. Darryl Quarles JASN 2007;18:1637-1647

FGF23 excess and related diseases

Hypophosphatemic rickets

- Autosomal dominant HR
  - FGF23 mutation
- Autosomal recessive HR
  - DMP1 inactivating mutation

FGF23 deficiency and related diseases



Familial tumoral calcinosis

Peri-articular, visceral and vascular calcifications

Biology: hyperphosphatemia, hypoparathyroidism

Genetics

- Recessive and dominant autosomal inheritance
- FGF23 inactivating mutation
- KLOTHO mutation : high FGF23 concentration

Japanese researchers reported Defect in Klotho gene expression in the mouse resulted in a syndrome that resembled Human ageing, including

- Short lifespan,
- Infertility
- Arteriosclerosis
- Skin atrophy
- Osteoporosis
- Emphysema

Nature 1997; 390: 45–51

Klotho-deficient mice and FGF23-deficient mice have an identical phenotype including

- Hyperphosphataemia
- Hypercalcaemia
- Elevated plasma calcitriol
- Vascular calcification
- Premature ageing

Nephrol Dial Transplant 2007; 22: 1524–1526

FGF23 Klotho and Phosphate metabolism

The bone–kidney endocrine axis mediated by FGF23 and Klotho has emerged as an essential component in the regulation of phosphate homeostasis

Nephrol Dial Transplant 2009;24: 1705–1708

When phosphate is in excess, FGF23 is secreted from bone , act on the kidney where Klotho is expressed

As a phosphaturic hormone, FGF23 reduces the amount (NaPi-2a) on the proximal tubules, promoting phosphate excretion

As a counter-regulatory hormone for vitamin D, FGF23 suppresses synthesis and promotes inactivation of 1,25-2(OH) D3 in proximal tubules

Nephrol Dial Transplant 2009;24: 1705–1708

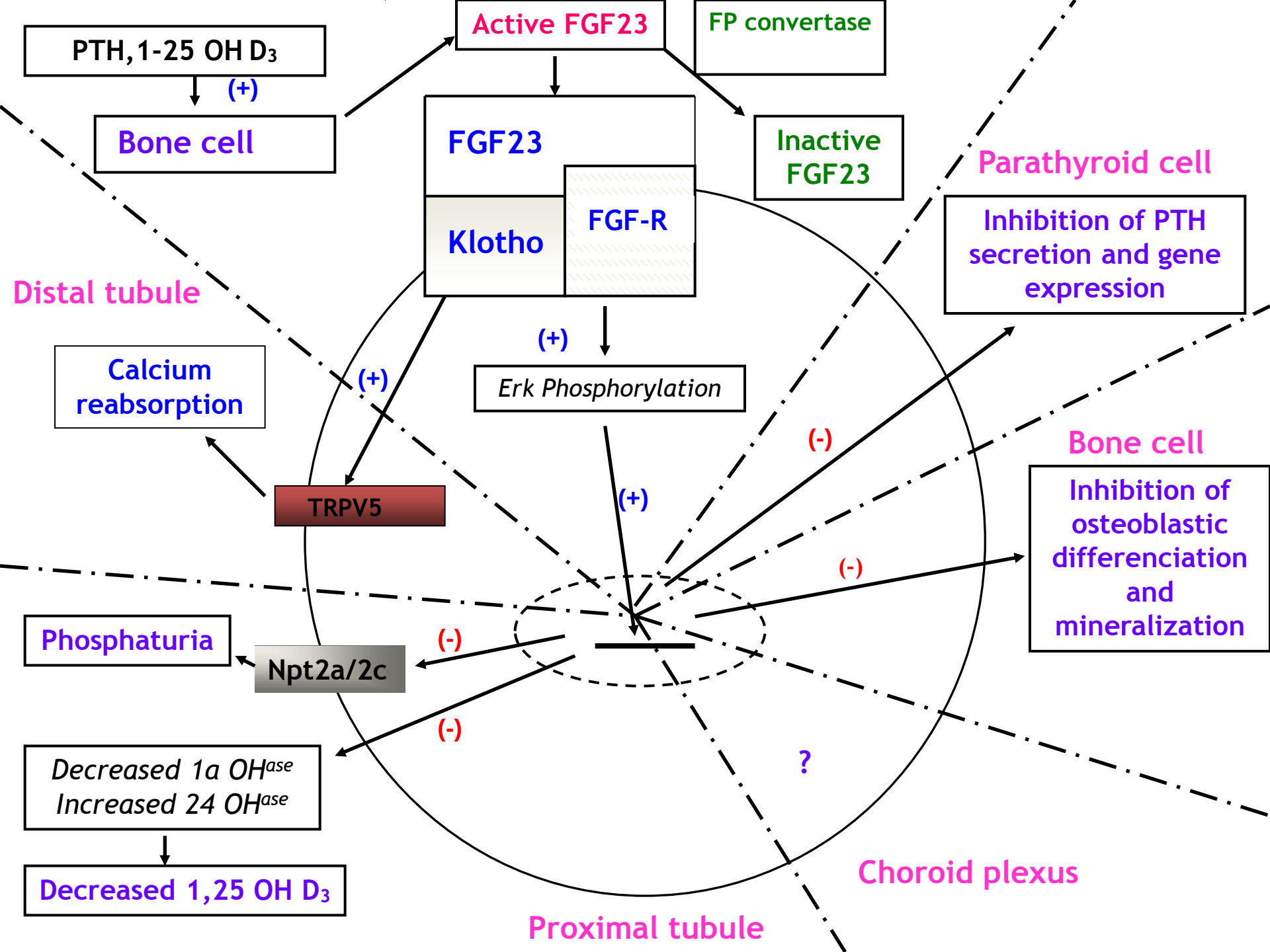
Klotho is involved in

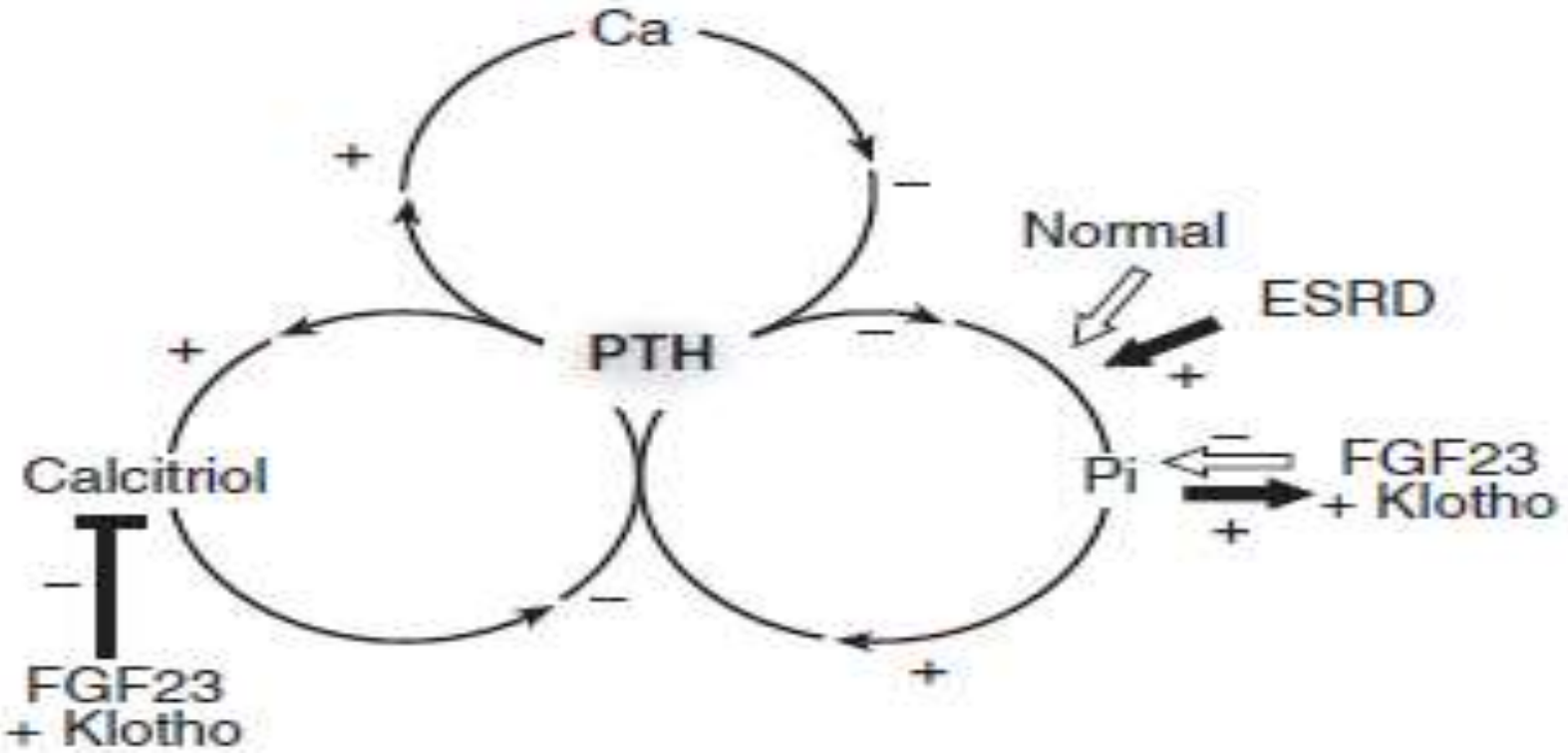
Renal control of calcium, phosphate and vitamin D Metabolism

Suppresses phosphate re-absorption in renal proximal tubule by binding to FGF receptors

Regulates Ca^{2+} re-absorption in the distal convoluted tubule by, stabilizing the TRPV5 Ca^{2+} channel in the plasma membrane

Nephrol Dial Transplant 2007; 22: 1524–1526


PTH, 1-25 OH D3
(+)
Bone cell
Active FGF23
FP convertase
FGF23
Inactive FGF23
Klotho
FGF-R
Parathyroid cell
Inhibition of PTH secretion and gene expression
Distal tubule
(+)
Calcium reabsorption
(+)
Erk Phosphorylation
(-)
Bone cell
TRPV5
(+)
Inhibition of osteoblastic differenciation and mineralization
(-)
Phosphaturia
(-)
Npt2a/2c
(-)
Decreased 1a OHase
Increased 24 OHase
?
Decreased 1,25 OH D3
Choroid plexus
Proximal tubule



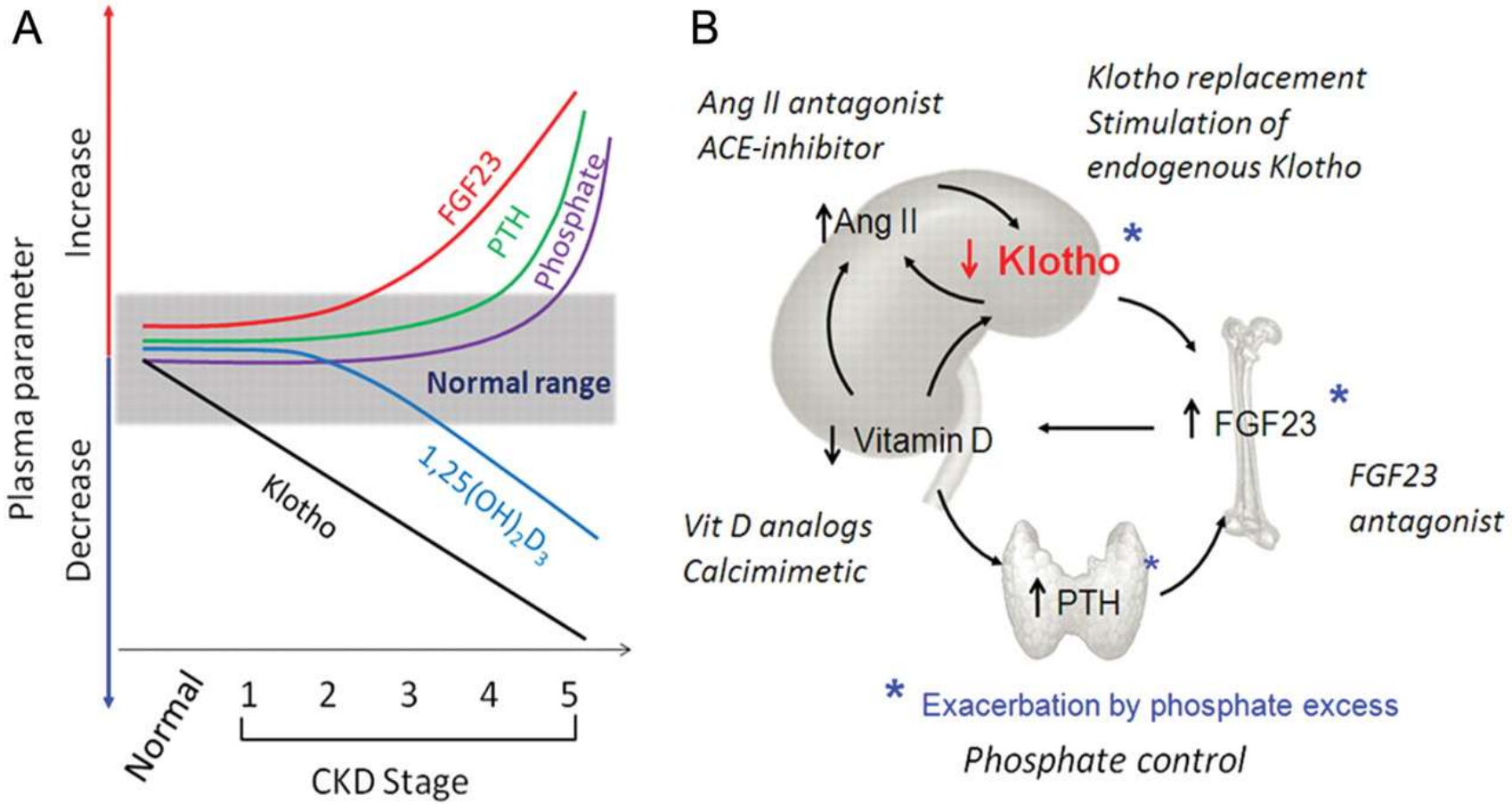
- FGF23 Klotho act synergistically with PTH to reduce tubular iP re absorption. However, FGF23 + Klotho inhibit tubular calcitriol synthesis, in contrast to PTH which stimulates it

Nephrol Dial Transplant 2007; 22: 1524–1526

Phosphate metabolism plays a critical role in the pathophysiology in CKD SO

Hyperphosphataemia should be aggressively treated to improve life expectancy of CKD patients

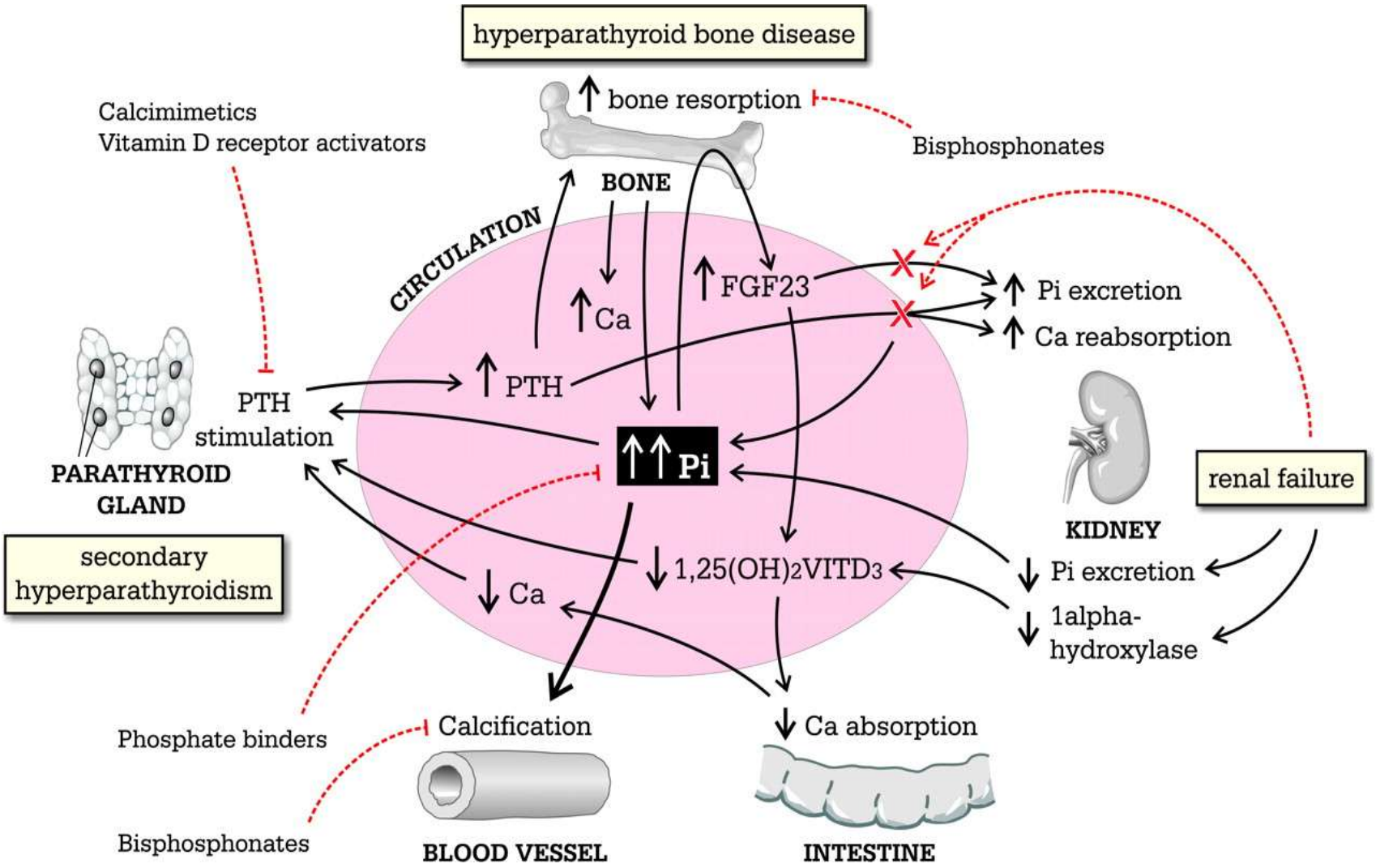
Proposed time profile of disturbances in mineral metabolism and phosphate-regulating hormones and therapeutic strategies in CKD. (A) Changes in parameters of mineral metabolism with CKD progression.



Hu M C et al. Nephrol. Dial. Transplant. 2012;27:2650-2657

NDT
Nephrology Dialysis Transplantation

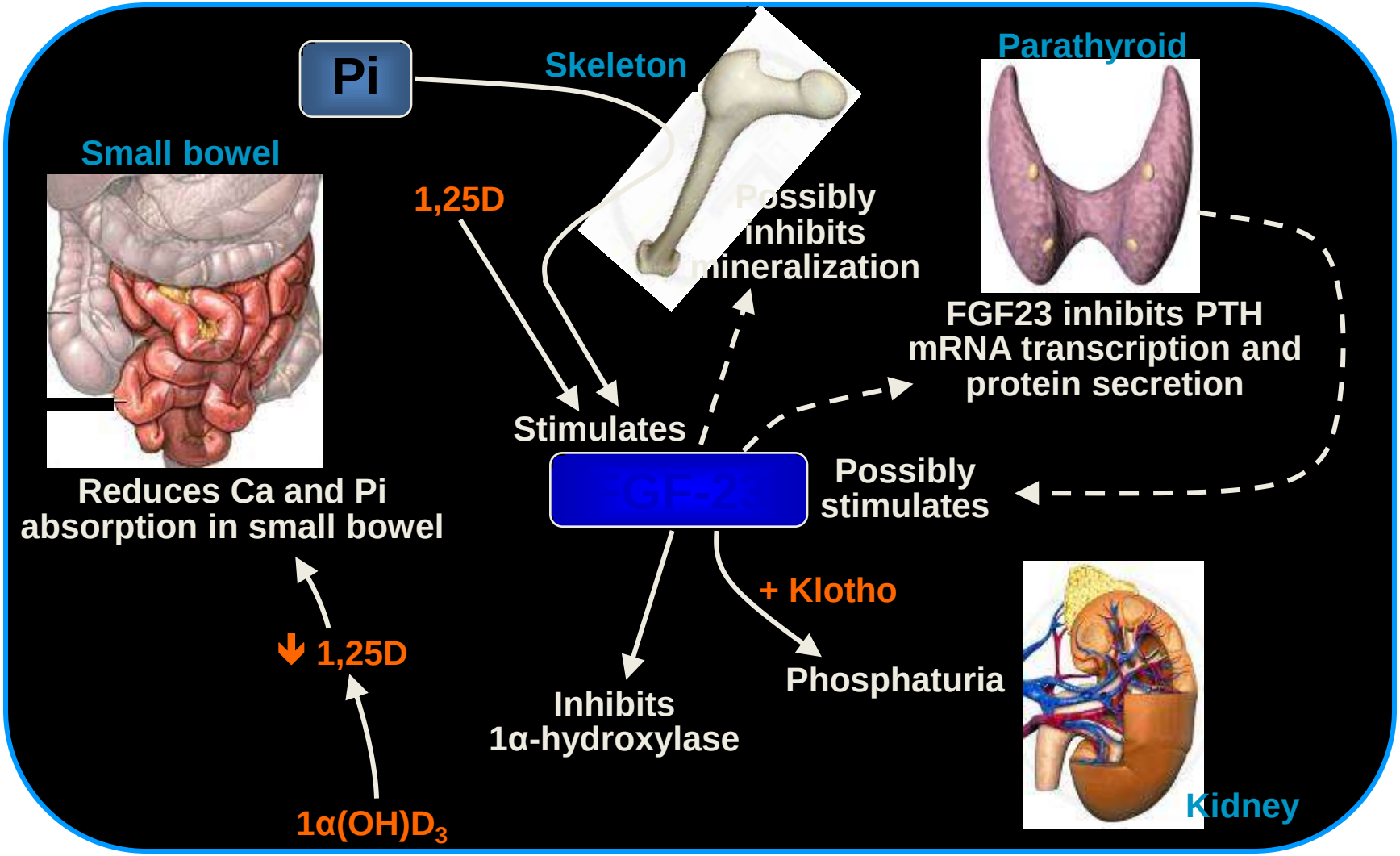
Disturbed mineral metabolism in CKD patients and the central role of hyperphosphatemia.



Neven E , and D'Haese P C Circulation Research 2011;108:249-264

American Heart Association
Learn and Live

FGF-23/Klotho: New players in CKD-MBD



Kuro-o. Keynote lecture from ERA-EDTA 2008, ASN 2008

Adapted from: Emmett M, et al. Kidney International 2008;73:3–5

These observations suggest that Klotho deficiency may contribute to pathophysiology of CKD

Recent animal studies have shown that

Klotho functions as a renoprotective factor

Although the mechanism remains to be determined, over-expression of Klotho ameliorated progressive renal injury in mouse models of AKI and GN

Nephrol Dial Transplant 2009;24: 1705–1708

Thus, decrease in Klotho expression potentially accelerates renal damage

Because 1,25- dihydroxyvitamin D3 increases Klotho expression in kidney, vitamin D treatment may be useful for interrupting this vicious cycle

Nephrol Dial Transplant 2009;24: 1705–1708

Surprisngly, serum FGF23 levels may increase before elevated serum phosphate level during the progression of CKD suggesting that Resistance to FGF23 may be one of the earliest changes in phosphate metabolism in CKD

It can be caused by a decrease in renal Klotho expression

Nephrol Dial Transplant 2009;24: 1705–1708

Fibroblast Growth Factor 23 (FGF23) Predicts Progression of Chronic Kidney Disease: The Mild to Moderate Kidney Disease (MMKD) Study

Danilo Fliser ,*Barbara Kollerits ,Ulrich Neyer ,Donna P. Ankerst,
Karl Lhotta ,Arno Lingenhel ,Eberhard Ritz ,Florian Kronenberg
MMKD Study Group(may 2007)

Assessed various parameters of calcium-phosphate metabolism including c-terminal and biologically active intact FGF23 plasma concentrations in 227 patients who had primary CKD.

177 of whom were prospectively followed for a median of 53 mo.

The study Identified

Intact FGF23 and,c-terminal FGF23 fragment as novel predictors of CKD progression.

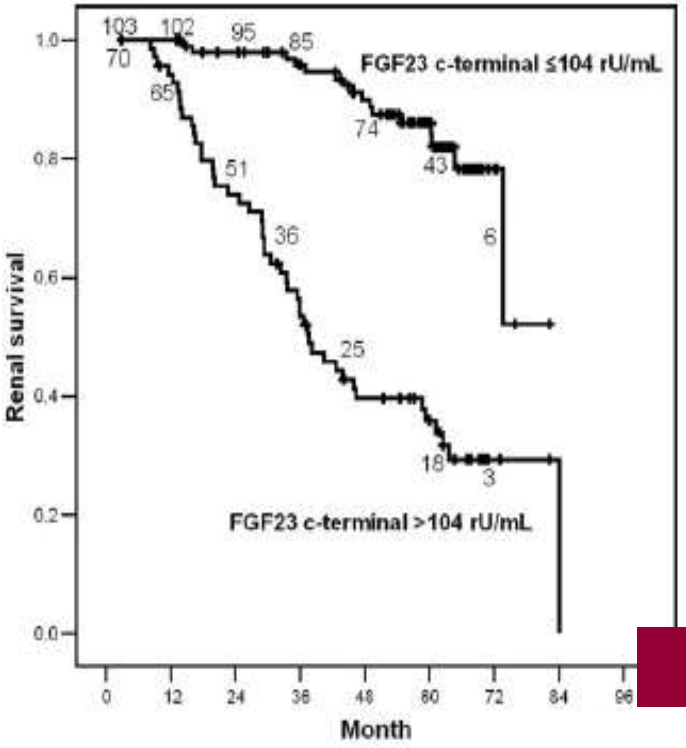
It may also serve as indicator of early alterations of calcium-phosphate metabolism,correction of which might modify progression of CKD possibly also cardiovascular risk

FGF23 and CKD in adult patients

FGF23: a novel independent **risk factor of progression** of CKD in 177 adult patients

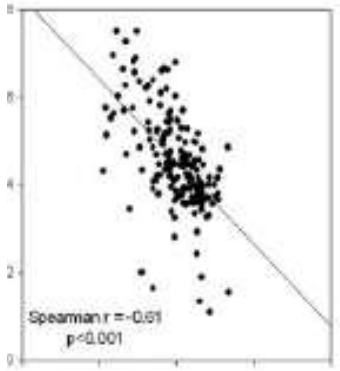
Prospective follow-up 53 months

Fliser *et al.*, JASN 2007

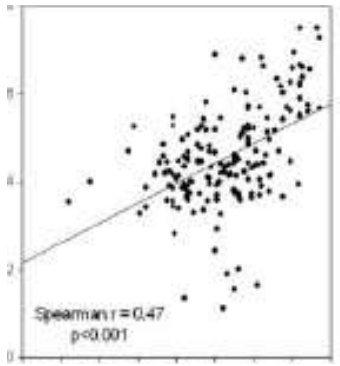


JASN

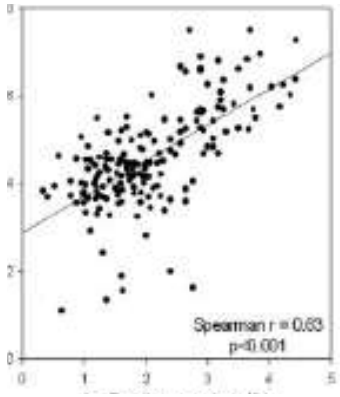
C-term FGF23



GFR



Phosphate



PTH

Reduced Renal α-Klotho Expression in CKD Patients and Its Effect on Renal Phosphate Handling and Vitamin D Metabolism

Hirokazu Sakan,Kimihiko Nakatani mail,Osamu Asai,Akihiro Imura,

Published: January 23, 2014

In summary, Renal dysfunction initially induces a reduction in renal tissue α-KL expression, which in turn reduces circulating sKL levels. This suggests that serum sKL concentration may be a useful marker of the renal α-KL level.

And also The secretion of FGF23 into the circulation is enhanced by renal failure-related high Pi at early stages of CKD

The resultant rise in FGF23 increased FEPi and reduced 1,25VitD .

This would in turn lead to normalization of serum Pi levels, despite falling renal α-KL expression.

In advanced CKD, by contrast, levels of α-KL are not sufficient to support renal FGF23-α-KL signaling

So FGF23 cannot compensate for the renal failure-induced Pi retention. Consequently, serum Pi is elevated, which would stimulate further increases in FGF23 secretion.

It is thus important to assess renal α-KL expression in CKD patients for appropriate management of serum FGF23 levels .

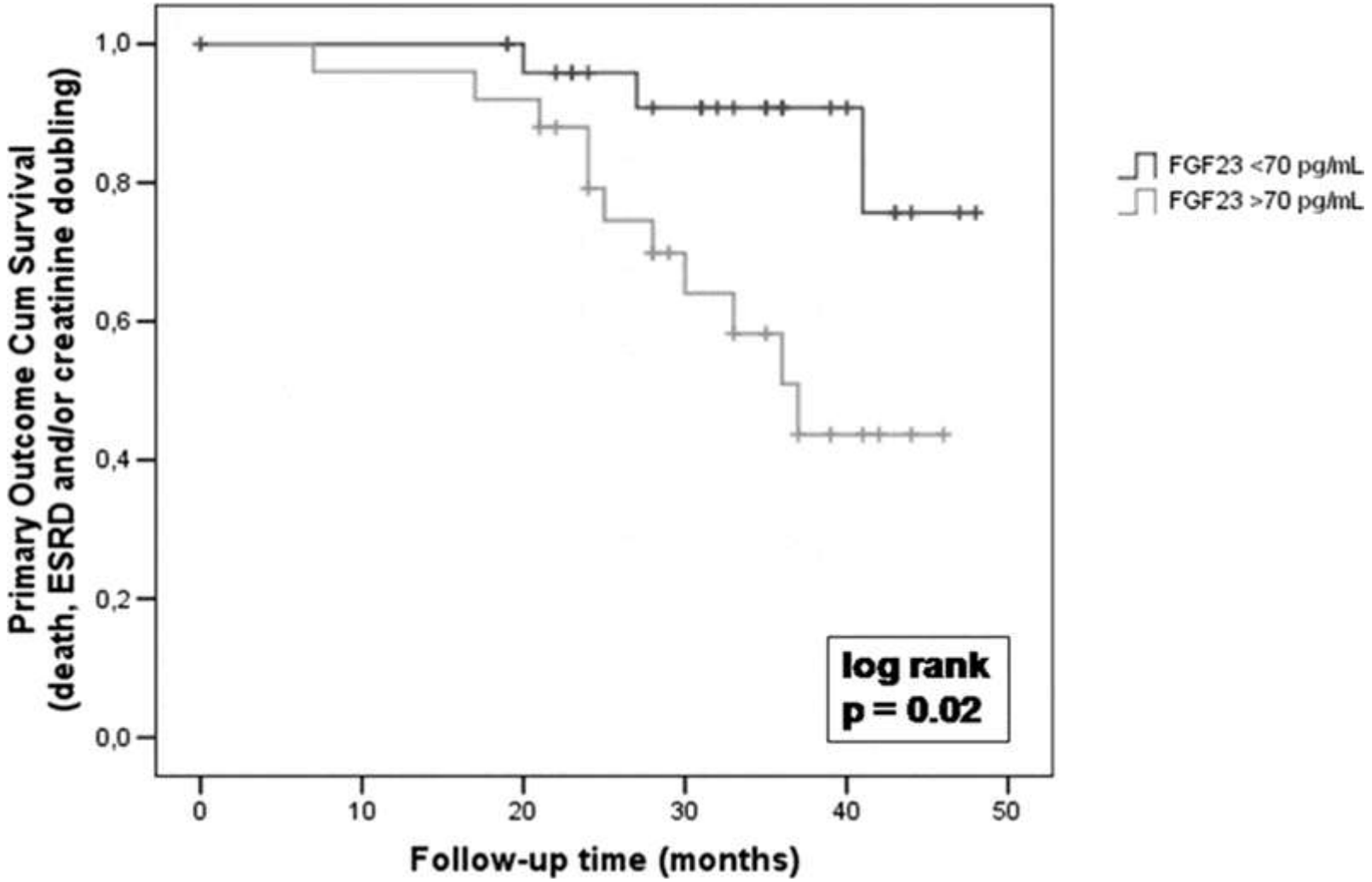
FGF-23 as a Predictor of Renal Outcome in Diabetic Nephropathy

Silvia M. Titan ,Roberto Zatz ,Fabiana G. Graciolli ,Luciene M. dos Reis,
Rui T. Barros ,Vanda Jorgetti ,Rosa M.A. Moysés(JASN 2011)

FGF-23 has been shown to independently predict CKD progression in nondiabetic renal disease.

Analyzed the relation between FGF-23 and renal outcome in diabetic nephropathy

Kaplan-Meier curves of the incidence of the composite primary outcome according to serum FGF-23 in 55 diabetic nephropathy patients.



Titan S M et al. CJASN 2011;6:241-247

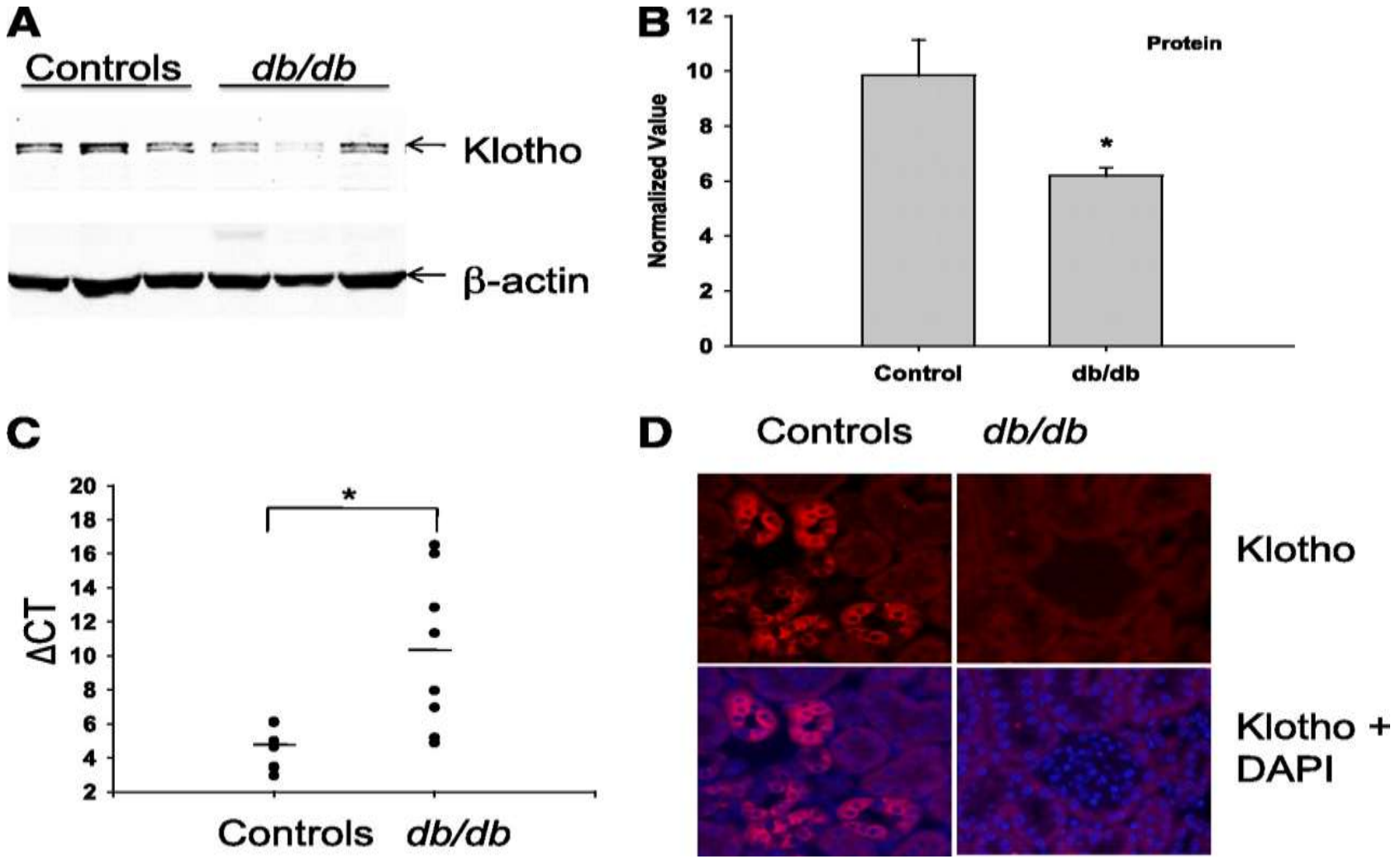
CJASN

In conclusion, data suggest that serum FGF-23 is a significant independent predictor of renal outcome in patients with macroalbuminuric DN. Further studies should clarify whether this relationship is causal and whether FGF-23 should be a new target for therapeutic measures aiming at DKD prevention

Klotho Depletion Contributes to Increased Inflammation in Kidney of the *db/db* Mouse Model of Diabetes via RelA(Serine)536 phosphorylation

Renal Klotho mRNA and protein were significantly decreased in *db/db mice*, and a similar decline was observed in the primary cultures of mouse tubule epithelial cells

Diabetes decreases Klotho protein and message in db/db mice.



Zhao Y et al. Diabetes 2011;60:1907-1916

The exogenous addition of soluble Klotho or overexpression of membranous Klotho in tissue culture suppressed NF-κB activation and subsequent production of inflammatory cytokines in response to TNF-α stimulation

In conclusion, Klotho has an anti-inflammatory function in the kidney and can offer resistance to oxidative stress.

Thus, an adequate tissue level of Klotho may provide dual protection against both oxidative stress and inflammation, while loss of Klotho increased oxidative stress, NF-κB activation

Clin Biochem .Nov;45(16-17):1415-20. doi: 10.1016/j.clinbiochem.2012.07.098. Epub 2012 Jul 23.

Soluble serum Klotho in diabetic nephropathy: relationship to VEGF-

Kacso IM ,Bondor CI ,Kacso G

In diabetic patients, Klotho is decreased in early CKD paralleling reduced GFR.

VEGF-A is higher in diabetic patients than in controls.

Both Klotho and VEGF-A are decreased in the presence of diabetic microalbuminuria. In

RESEARCH ARTICLE

Risk of ESRD and All Cause Mortality in Type 2 Diabetes According to Circulating Levels of FGF-23 and TNFR1

Jung Eun Lee,Tomohito Gohda,William H. Walker,Jan Skupien,Adam M. Smiles,

Published: March 20, 2013

This study aims to examine whether the predictive effect of FGF-23 is independent from circulating levels of tumor necrosis factor receptor 1 (TNFR1), a strong predictor of ESRD in Type 2 diabetes)

Conclusion

The effect of circulating levels of FGF-23 on the risk of ESRD is accounted for by circulating levels of TNF

Circulating levels of FGF-23 have an independent effect on all-cause mortality in T2D.

Renal expression of FGF23 in progressive renal disease of diabetes and the effect of ace inhibitor.

Zanchi C, Locatelli M, Benigni A, Corna D, Tomasoni S, Rottoli D, Gaspari F, Remuzzi G, Zoja C (PloS 1 2013)

To evaluate whether the renoprotective effect of angiotensin converting enzyme (ACE) inhibitor was associated with changes in FGF23 and Klotho

FGF23 became measurable in the kidney of diabetic rats at 4 months and significantly increased thereafter. FGF23 protein localized in proximal and distal tubules .

Ramipril limited proteinuria and renal injury, attenuated renal FGF23 upregulation

suggesting another mode of action of ace on DN

- **Fibroblast Growth Factor 23 (FGF23) Levels, Phosphate Intake and its Association with Indices of Renal Handling of Phosphate in Healthy Volunteers**
- Noreen Abbas, Aysha Habib Khan*, Farooq Ghani and Imran Siddiqu

Published: January 20, 2016

- FGF23 is also connected to hypertension, obesity and metabolic syndrome . this would represent a key paradigm move that changed FGF23 from biomarker to mechanism of disease, and raises the option of FGF23 being a primary target for intervention

Conclusions

FGF23

- Is a new hormone predominately expressed in osteocytes

Klotho

- Is a transmembrane protein that is required for FGF23-mediated receptor

Klotho functions as an obligatory coreceptor for FGF23

Klotho-FGFR coexpression likely defines the tissue specificity of FGF23 effects

FGF23, in the absence of klotho, cannot exert its bioactivities

The bone-kidney endocrine axis mediated by FGF23 -Klotho is essential for the regulation of phosphate homeostasis

FGF23 - Klotho plays a central role in the pathogenesis of altered mineral metabolism and secondary hyperparathyroidism in CKD patients

FGF23 - Klotho can be used not only as a biomarker for assessing phosphate retention but also as a predictor of mortality and future development of refractory hyperparathyroidism

Further elucidation of FGF23 function and regulation will help to establish a rational for the management of the mineral and bone disorders that are associated with high morbidity and mortality and in CKD patients

Thank You!